REMARKS

Applicants appreciate the allowance of Claims 14 and 68 and the withdrawal of a number of the prior pending rejections.

In an effort to expedite the present case, Applicants have canceled Claims 4, 15, 55, 61 and 65 without prejudice or disclaimer.

Applicants have the following comments in response to the Office Action.

Novel Composition of Matter

Amended independent Claims 1, 10 and 51 are directed to radiosensitizer agents that contain a certain highly-halogenated halogenated xanthene, specifically disodium 4,5,6,7-Tetrabromo-erythrosin. This particular compound is explicitly disclosed, for example, in Table I of Applicants' original specification. Applicants believe that they are the first to conceive of this compound and do not believe that the compound is described in any prior art reference. As explained *infra,* there is no disclosure of this compound in the cited references nor any suggestion of this compound.

The novelty of this compound is the result, at least in part, of the relative complexity of synthesis that is posed by steric hindrance[1] from the dense content of halogens, along with other factors such as photochemical instability that make the compound relatively difficult to produce, handle, store and use, and would also make the compound unattractive for conventional use of this class of molecule as a dyestuff. Applicants submit that they are the first to invent the claimed compound which represents a novel extension to the halogenated xanthene family. For example, Rose Bengal (a very stable molecule which formerly comprised the most halogen-rich member of

[1] Steric hindrance is spatial interference inhibiting or preventing the close arrangement of adjacent atoms within a molecule due to the sizes of the overlapping electron clouds of the adjacent atoms, and poses particularly difficult synthetic challenges when large atoms, such as bromine and iodine, are incorporated into a molecule.

the halogenated xanthene family) has been known for over 100 years. Nonetheless, knowledge of its properties and those of the other previously known halogenated xanthenes (such as Phloxine B, Erythrosin, and Eosin) has not led those skilled in the art (prior to Applicants' conception) to conceive, suggest, synthesize or investigate Applicants' claimed highly-halogenated halogenated xanthene, disodium 4,5,6,7-Tetrabromoerythrosin. Nor has anyone else conceived of pharmaceutical compositions consisting of any halogenated xanthene for therapeutic use as a radiosensitizer prior to Applicants' work.

Disodium 4,5,6,7-Tetrabromoerythrosin is a derivative of fluorescein that is the result of a highly specific pattern of chemical substitution. It is highly unlikely one skilled in the art would have arrived at such a compound, unless one already knew the compound or conceived of Applicants' novel application for such a compound. Furthermore, this compound is the result of combination of highly specialized starting materials combined in a specific way. For example, synthesis of disodium 4,5,6,7-Tetrabromoerythrosin involves condensation of resorcinol with tetrabromophthalic anhydride, followed by iodination of the resulting intermediate with I_2 and saponification of the acid form to the disodium salt. Since tetrabromophthalic anhydride is not a standard compound, this starting material itself would require custom synthesis. Once the compound is known, this would be clear to one skilled in the art. It would be nearly impossible, however, to start with a broad, general disclosure, such as that of any known prior art, and then arrive at the claimed compound.

As further evidence of the novelty of Applicants' claimed composition, the Examiner's attention is directed to the Colour Index,[2] which is a definitive compendium of known dyes. The

[2] A copy of the cited section of the Colour Index is supplied with the enclosed IDS. The Colour Index is referenced in Heitz (US 4,846,789) which is already of record. In the current Office Action, the Examiner states that the anticipation rejection over Heitz has now been

section on fluorescein derivatives (pp. 4424-4428, CI nos. 45350-45445) lists approximately 39 compounds in the same general class of molecules as that of disodium 4,5,6,7-Tetrabromoerythrosin. Moreover, this listing encompasses the majority of the specific example compounds enumerated in the prior art cited by the Examiner in this Office Action.

The fluorescein analogs listed in the Colour Index contain various heteroatoms (such as halogens) or functionalities (such as hydroxyl, carboxyl, alkyl, aryl, nitro or thiol groups) at the 4, 5, 6, 7, 2', 4', 5' and 7' positions. Some of these analogs, such as Phloxine B and Rose Bengal, contain halogens at each of these positions. However, whereas Applicants' claimed halogenated xanthene require substitution of fluorescein at the 2', 4', 5' and 7' positions with 4 atoms of iodine and at the 4, 5, 6 and 7 positions with 4 atoms of bromine, *no such compound* is represented in the Colour Index. Furthermore, despite the lengthy, comprehensive listing of compounds in the Colour Index, only five of the compounds listed therein have more that 4 halogens at any combination of these positions, and none of these contain both iodine and bromine, as in the claimed compound. Thus, the Colour Index does not disclose Applicants' claimed compound or any closely related compounds.

Clearly the prior art (as exemplified by the Colour Index) does not describe Applicants' claimed compound nor any compound remotely similar to Applicants' claimed compound. For example, none of the known prior art describes any fluorescein derivative that contains four iodine atoms at positions 2', 4', 5' and 7' *along with* even one bromine atom at any of positions 4, 5, 6 or 7, as in Applicants' claimed compound. Thus, the prior art does not disclose or suggest Applicants' novel compound disodium 4,5,6,7-Tetrabromoerythrosin, which is the basis for the claimed pharmaceutical compositions.

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withdrawn.

Applicants conceived of this new compound in an effort to improve radiosensitizer efficiency for treatment of diseases of human tissue, the performance of which may be enhanced by increasing the halogen density of the halogenated xanthene molecules, for example by including greater numbers of halogen atoms or increasing their atomic number. A consequence of such enrichment is greatly reduced stability of the xanthene molecule, especially upon exposure to optical radiation. Such trends in synthetic complexity and instability run counter to the teachings of the prior art which are predicated on use of inexpensive, relatively stable molecules as dyes or as fluorophors. Since such dyes and fluorophors generally must be stable in the presence of light (a dye is of dubious value if it must be kept and used in the dark since it requires light to be seen), prior investigators had no reason and were not motivated to consider or investigate, and there is no evidence that they conceived of or considered, Applicants' novel compound since this compound would have no obvious relevance for the uses employed by such investigators.

Accordingly, the claimed highly-halogenated halogenated xanthene, disodium 4,5,6,7-Tetrabromoerythrosin, and the various claimed pharmaceutical compositions containing such halogenated xanthene, of the claims of the present application are novel over the prior art.

Obviousness Double Patenting

In the Office Action, the Examiner provisionally rejects Claims 1, 4, 10, 15, 51, 52, 55-57, 61, 65 and 66 for alleged obviousness-type double patenting over claims 1, 2, 9, 10, 11, 19, 27, 36 and 37 of copending U.S. application no. 09/900,355 in view of Widholz et al. (Merck Index 1983). This provisional rejection is respectfully traversed.

While Applicants traverse this rejection (since, for example, the '355 application concerns certain chemotherapeutic medicaments and methods, whereas the current application concerns

radiosensitizer agents, and whereas Widholz does not disclose nor suggest disodium 4,5,6,7-Tetrabromoerythrosin), in order to advance the prosecution of this application, Applicants are submitting herewith a terminal disclaimer and fee with regard to the '355 application. Accordingly, it is respectfully submitted that this rejection has been overcome, and it is requested that the rejection be withdrawn.

Claim Rejections – 35 USC §102

Kim

The Examiner rejects Claims 1, 10, 51, 52, 56, 57 and 66 under 35 U.S.C. §102(b) for alleged anticipation by Kim et al. (JP 06-128128). This rejection is also respectfully traversed.

First, as explained *supra*, the radiosensitizer agents of the claims of the present application are comprised of certain formulations of disodium 4,5,6,7-Tetrabromoerythrosin, which is a *novel and non-obvious composition of matter*.

Clearly, Kim does not expressly disclose disodium 4,5,6,7-Tetrabromoerythrosin. For example, this compound is missing from the lengthy lists of compounds disclosed by Kim on p. 2, paragraph 0013 and on p. 3, paragraph 0021. Further, in reference to Formula I of Kim, none of the compounds enumerated in these lists is believed to contain one or more iodine atoms at any position X and one or more bromine atoms at any position Y, whereas Applicants' claimed disodium 4,5,6,7-Tetrabromoerythrosin contains only iodine at each position X and only bromine at each position Y. Moreover, using the generic description of compounds provided by Kim in the abstract, Applicants believe that there are over 100,000 potential combinations of the enumerated elements, only one of which could be manipulated to correspond to Applicants' claimed disodium 4,5,6,7-Tetrabromo-erythrosin. However, this is improper for an anticipation rejection.

More specifically, as discussed above, it cannot be disputed that Kim does not specifically disclose Applicants' claimed compound. The Examiner, however, cites Kim as disclosing "halogenated xanthene dyes represented by Formula I ... [the] structure of which is consonant to 4,5,6,7-Tetrabromoerythrosin" and uses this as the apparent basis for the anticipation rejection of Applicants' claims. Such a rejection is improper under the patent rules. As Applicants explained previously, MPEP §2132.02 states that:

> **"A GENERIC CHEMICAL FORMULA WILL ANTICIPATE A CLAIMED SPECIES COVERED BY THE FORMULA WHEN THE SPECIES CAN BE "AT ONCE ENVISAGED" FROM THE FORMULA**
> When the compound is not specifically named, but instead it is necessary to select portions of teachings within a reference and combine them, e.g., select various substituents from a list of alternatives given for placement at specific sites on a generic chemical formula to arrive at a specific composition, anticipation can only be found if the classes of substituents are sufficiently limited or well delineated. *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990). If one of ordinary skill in the art is able to "at once envisage" the specific compound within the generic chemical formula, the compound is anticipated. One of ordinary skill in the art must be able to draw the structural formula or write the name of each of the compounds included in the generic formula before any of the compounds can be "at once envisaged." One may look to the preferred embodiments to determine which compounds can be anticipated. *In re Petering*, 301 F.2d 676, 133 USPQ 275 (CCPA 1962)."

In the present case, Kim discloses in the Abstract and Formula I, which is relied upon by the Examiner in the Office Action, "halogenated fluorescein dyes represented by formula I or II, (wherein X is H, Cl, Br or I, at least two of four X's are not H, Y is H, Cl or Br and M is H, Na or K)...." Hence, Kim is discussing the possibility of substitution at each of 10 positions with a multiplicity of different elements, the potential combinations of which run well over 100,000. This is hardly the limited class discussed in MPEP 2131.02 and is clearly not the situation where one skilled in the art could at once envisage the claimed compound of the present application. Only through the use of hindsight reconstruction using the claimed compound as a blue print or endless experimentation (which would likely take lifetimes) could one skilled in the art arrive at the claimed

compound from this disclosure in Kim. Therefore, in accordance with MPEP 2131.02, Kim cannot be said to describe or anticipate the claimed compound.

Moreover, since Kim concerns certain cosmetic preparations used as hair dyes, neither Kim nor one of skill in the art upon reading Kim would be led to Applicants' claimed compound nor to Applicants' claimed therapeutic agents and compositions. Presumably, the hair dyes of Kim must be inexpensive and stable upon exposure to light, key features which disodium 4,5,6,7-Tetrabromo-erythrosin presumably does not offer, as described *supra*.

For at least the aforementioned reasons Kim does not disclose nor anticipate the claimed compound, nor the therapeutic agents or compositions, of the present application. Accordingly, it is respectfully requested that this rejection be withdrawn.

Patel

The Examiner also rejects Claims 1, 10, 51, 52, 56, 57 and 66 under 35 U.S.C. §102(b) for alleged anticipation by Patel (EP 0 064 012). This rejection is also respectfully traversed.

As explained *supra* with regard to Kim, the radiosensitizer agents of the claims of the present application are comprised of certain formulations of disodium 4,5,6,7-Tetrabromoerythrosin, which is a *novel and non-obvious composition of matter*.

Clearly, Patel does not expressly disclose disodium 4,5,6,7-Tetrabromoerythrosin. For example, this compound is missing from the list of compounds disclosed by Patel on p. 5, lns. 11-18. Referring to this list and to Formula II of Patel, none of the compounds enumerated in this list contains one or more iodine atoms at any position X and one or more bromine atoms at any position Y, whereas Applicants' claimed disodium 4,5,6,7-Tetrabromoerythrosin contains only iodine at each position X and only bromine at each position Y. Moreover, using the generic description of

compounds provided by Patel in reference to Formula II (p. 4, ln. 12 - p. 5, ln. 10), Applicants believe that there are *over 63 million* potential combinations of the enumerated functionalities, only one of which can be manipulated to correspond to Applicants' claimed disodium 4,5,6,7-Tetrabromoerythrosin. However, this is improper for an anticipation rejection.

More specifically, as discussed above, Patel clearly does not specifically disclose Applicants' claimed compound. With regard to the generic Formula II of Patel, under the patent rules, the 63 million possibilities represented thereby certainly does not anticipate Applicants' claimed compound and is not the proper basis for an anticipation rejection. Accordingly, it is respectfully submitted that such a rejection is improper under the patent rules, as the disclosure of Patel is not the limited class discussed in MPEP 2131.02, and is clearly not the situation where one skilled in the art could at once envisage the claimed compound of the present application. Only through the use of hindsight reconstruction using the claimed compound as a blue print or endless experimentation (which would take many, many lifetimes) could one skilled in the art arrive at the claimed compound from this disclosure in Patel. Therefore, in accordance with MPEP 2131.02, Patel cannot be said to describe or anticipate the claimed compound.

Moreover, whereas Patel concerns certain epoxy catalyst systems, while Applicants' claimed invention concerns therapeutic agents and compositions for radiosensitization, neither Patel nor one of skill in the art upon reading Patel would be led to Applicants' claimed invention.

For at least the aforementioned reasons Patel does not disclose nor anticipate the claimed compound, nor the therapeutic agents or compositions, of the present application. Accordingly, it is respectfully requested that this rejection be withdrawn.

Claim Rejections – 35 USC § 103(a)

The Examiner also rejects Claims 4, 15, 55, 61 and 65 under 35 U.S.C. §103(a) for allegedly being unpatentable over Kim or Patel in view of Williams et al. (US 5,576,013). While this rejection is also respectfully traversed, in order to advance the prosecution of this application, Applicants have canceled the rejected claims without prejudice or disclaimer, rendering this rejection moot.

Accordingly, it is requested that this rejection be withdrawn.

Allowable Subject Matter

The Examiner has deemed Claims 14 and 68 to contain allowable subject matter. Such allowance is gratefully acknowledged.

Conclusion

For at least the above-stated reasons, it is respectfully submitted that the claims of the present application are in an allowable form and are patentable over the cited references. Accordingly, this application should be allowed.

If any fee should be due for this Amendment, the terminal disclaimer, or the extension of time, please charge our deposit account 50/1039.

Favorable reconsideration is earnestly solicited.

Respectfully submitted,

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